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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/972,245	10/09/2001	Joseph Roberts	078728-0104	3976

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EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 08/12/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/972,245	ROBERTS ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 June 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-40* is/are pending in the application.

4a) Of the above claim(s) *14-16 and 23-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-13 and 17-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 January 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/31/03, 6/5/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

An amendment was received on 6/1/04.

Claims 1-40 remain pending in the Application. Claims 1-13 and 17-22 are under consideration in this Office Action. Claims 14-16 and 23-40 are withdrawn as being drawn to non-elected subject matter. Linking claims 1-6 and 17-19 are considered to the extent that they embrace the elected invention.

Priority

A petition to claim benefit to a provisional application (60/239,268), and appropriate fee, were received and entered on 6/1/04. Applicant's submission satisfies 37 CFR 1.78. The effective filing date of the instant application is considered to be 10/12/2000.

Rejections Withdrawn

The rejection of claim 5 as indefinite is withdrawn in view of Applicant's arguments showing a definition in the paragraph bridging pages 5 and 6 of the specification.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 5-13, and 17-21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, 2, 5-13, and 17-21 are drawn to the genus of methods of determining modification conditions of a therapeutic agent to prevent host-mediated inactivation of the therapeutic agent. The claims do not recite the intended breadth of the term "modification". It is apparent to one of ordinary skill in the art that a variety of drug modifications are known, both of covalent and non-covalent nature. For example, modification of anionic drugs by complexation with polycations is known in the art, as is covalent derivatization with functional groups (e.g. alkyl, acyl, phosphate, etc.). Such processes are performed in a variety of conditions. However, the specification fails to provide any correlation between the structure of the modifying group, and the intended modifying group, the conditions employed, and the intended nature/outcome of a representative number of species of modifications, thereby leading to protection from host-mediated inactivation.

Adequate written description of a genus may be attained by description of a representative number of species of the genus, either by reduction to practice, drawings, or description of relevant identifying characteristics, e.g. disclosure of a correlation between some structural feature common to the species of the claimed genus and the desired function. The specification reduces to practice the modification of

therapeutic agents by covalent attachment of polyethylene glycol (PEG) moieties, and generally discloses covalent modification with biocompatible polymers, but fails to describe any other modification process or conditions directly or by relevant identifying characteristics. Thus one of skill in the art could not conclude that Applicant was in possession of modifying elements and conditions that achieve the desired result, other than those required for covalent attachment of biocompatible polymers, at the time of the invention. As such, the scope of the newly amended claims should be limited to methods of determining reaction conditions for covalent modification of a therapeutic agent with a biocompatible polymer to prevent host mediated inactivation of said therapeutic agent when covalently modified by said biocompatible polymer.

Response to Arguments

Applicant's arguments filed 6/1/04 have been fully considered but they are not persuasive.

Applicant argues at pages 8 and 9 of the response that the specification the description adequately supports the phrase "modification conditions" because it describes parameters including they type of polymer linked or joined to the therapeutic agent, the extent of modification, and the conditions of modification. This is unpersuasive because the specification places no limit on the genus of modifications embraced, and the specification limits only the type of modifying agent, i.e. a biocompatible polymer, and not the type of modification that may be performed with it, i.e. covalent or non-covalent (ionic interaction, encapsulation, incorporation into a

microsphere, etc.). However, the description in the specification is limited to covalent modification of amino acids of a therapeutic agent by covalent attachment of a biocompatible polymer. Furthermore the claims recite no limitation on modification conditions, listing only steps for comparing modified agents. As such, the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 5-7, 9, 10, 12, 13, and 17 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Alvarez et al ((Med. Pediatr. Oncol. 34(3): 200-205, 2000) in view of Graham et al (Bone Marrow Transplant (21(9): 879-885, 1998), Abshire et al (Clin. Obs. Interven. Therap. Trials (Blood 96(5): 1709-1715, 9/1/2000), and Francis et al (Int. J. Hematol. 68(1): 1-18, 1998).

Alvarez discloses a comparative study of the effects of pegylated asparaginase relative to those of native asparaginase. Pegylated asparaginase caused toxicity including nausea, vomiting and pancreatitis in greater than half of recipients being treated for ALL. Patients were monitored by sequential serum amylase and lipase determinations.

Alvarez does not teach the comparison of two different types of pegylated asparaginase. Alvarez is silent as to the number of injections of pegylated and native asparaginases.

Graham discloses a clinical trial of pegylated asparaginase in the treatment of acute lymphoblastic leukemia (ALL). Patients received between 1 and 12 doses of pegylated asparaginase. Patients were monitored for relapse throughout the course of treatment. This is considered to amount to an assay of biological activity of the drug. Most of the patients who received the drug developed toxicities which resulted in abbreviated courses of administration. Symptoms included nausea, vomiting, and pancreatitis. See abstract. Evaluations of toxicity are also considered to be measurements of biological activity.

Abshire et al (Clin. Obs. Interven. Therap. Trials (Blood 96(5): 1709-1715, 9/1/2000) taught that pegylated asparaginase showed prolonged half-life and reduced immunogenicity compared to native asparaginase. See paragraph bridging columns 1 and 2 on page 1709.

Francis teaches that pegylation of protein drugs can cause can cause toxicity. See sentence bridging columns 1 and 2 on page 4, and first sentence of paragraph bridging pages 7 and 8. Francis also teaches that bioactivity, stability, immunogenicity, and toxicity may be affected by the way in which a protein drug is pegylated. See abstract, and pages 2-4. Important considerations include the site of attachment of PEG, the degree of modification, the coupling chemistry chosen, the presence or absence of a linker, and generation of harmful co-products. See page 3, column 2, first

full paragraph. Francis teaches that the appropriate pegylation method is generally determined empirically by examining a range of different degrees of substitution, as well as different coupling techniques. See page 6, column 1, first full paragraph. The bioactivity retention and other functions of the products may be assessed as a mixture, or individual members of a pegylation series may be assayed individually. See e.g. page 6, first full paragraph of column 1.

At the time the invention was made, pegylation of asparaginase was seen to have both advantages (increased half-life and reduced immunogenicity) and disadvantages (increased toxicity). It would have been obvious to one of ordinary skill in the art at the time of the invention to produce a variety of differently pegylated versions of asparaginase, because Francis suggests that positive attributes of pegylated drugs can be maximized, while minimizing negative attributes, by determining the optimum pegylation conditions. See abstract. It would have been obvious to then compare and test the resulting pegylated forms of asparaginase. It is clear that it was routine in the art to compare different forms of asparaginase in head to head studies as taught by Alvarez. It would have been similarly obvious to measure the effects of the drugs after each injection, as patients undergoing treatment for ALL, such as those in the Graham and Alvarez studies, are continuously monitored for disease progress. Claim 5 is included in this rejection because in light of the teachings of Francis, the extent of pegylation is a result-effective variable that is routinely optimized by those of skill in the art. See page 3, column 2, first full paragraph. Claim 6 is included in this rejection because the selection of different coupling chemistries is part of the

optimization process suggested by Francis, and different chemistries result in different modifying agents. For example, in the TMPEG method discussed at page 5, the PEG is linked to the polypeptide directly without any linker, whereas other chemistries may cause the introduction of immunogenic groups (see e.g. page 4, column 1, lines 1-10 of first full paragraph.

Thus the invention as a whole was prima facie obvious.

Claim 4 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Alvarez, Graham, Abshire, and Francis, as applied to claims 1-3, 5-7, 9, 10, 12, 13, and 17 above, and further in view of Petersen et al (US Patent 6,531,122)

The teachings of Alvarez, Graham, Abshire, and Francis are summarized above and can be combined to render obvious methods of synthesizing and comparing differently pegylated asparaginases. Francis also teaches that one reaction chemistry known in the art for PEG modification utilizes a cyanuric chloride linker. See page 4, lines 5-9 of first full paragraph.

These references do not teach SBA-, SC-, and ALD-PEGs.

Petersen teaches that SBA-, SC-, and ALD-PEGs, as well as a variety of other types of modified PEGs, including those with a cyanuric chloride linker, may be used interchangeably to modify polypeptide drugs. See paragraph bridging pages 24 and 25; column 25, first full paragraph, especially, lines 12, 27, 28, and 30; and column 26, lines 36-42.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify asparaginase with any of SBA-, SC-, and ALD-PEGs, because these derivatives were well known equivalents in the prior art. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982).

Thus the invention as a whole was prima facie obvious.

Claims 8, 11, and 20-22 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Alvarez, Graham, Abshire, and Francis, as applied to claims 1-3, 5-7, 9, 10, 12, 13, and 17 above, and further in view of Roberts et al (J. Gen. Virol. 72:299-305,1991).

The teachings of Alvarez, Graham, Abshire, and Francis are summarized above and can be combined to render obvious methods of synthesizing and comparing differently pegylated asparaginases.

These references do not teach an enzyme used to treat viral infection, used to reduce glutamine levels, or asparaginase glutaminase from Pseudomonas.

Roberts teaches that glutaminase asparaginase from Pseudomonas can be used to treat retroviral disease by repeated administration, and that pegylation of the

enzyme increases its half-life several fold. See abstract, and page 304, penultimate sentence of column 1.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify Pseudomonas asparaginase glutaminase by pegylation. One would have been motivated to do so in order to increase its half-life in vivo and to decrease its immunogenicity, as taught by both Roberts and Francis. It would have been similarly obvious to optimize the pegylation conditions as taught by Francis. In doing so it would have been obvious to deliver differently pegylated forms of the enzyme in vivo over the course of treatment taught by Roberts. It would have been obvious to monitor the progress of the disease over the course of treatment in view of the teachings of Alvarez and Graham, who show that this is routine in the art.

Claims 18 and 19 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Alvarez, Graham, Abshire, and Francis, as applied to claims 1-3, 5-7, 9, 10, 12, 13, and 17 above, and further in view of Bollin et al (US Patent 4,678,812, issued 7/7/87).

The teachings of Alvarez, Graham, Abshire, and Francis are summarized above and can be combined to render obvious methods of synthesizing and comparing differently pegylated asparaginases.

These references do not teach adding an excipient that protects asparaginase during lyophilization.

Bollin teaches that proteins can be stabilized by lyophilization and that saccharides are useful in stabilizing asparaginase during lyophilization.

It would have been obvious to one of ordinary skill in the art to add saccharides to the pegylated asparaginases developed by the methods described above, for the purpose of stabilizing them during lyophilization. One would have been motivated to do so because Bollin teaches that proteins may be stabilized by lypohilization, and that asparaginase in particular is stabilized by addition of saccharides during lyophilization.

Thus the invention as a whole was prima facie obvious.

Response to Arguments

Applicant's arguments filed 6/1/04 have been fully considered but they are not persuasive.

Applicant addresses the 103 rejections at pages 10-12 of the response. Applicant argues that none of the cited references teaches assaying biological activity of the modified therapeutic agent after administration of a booster does of modified therapeutic agent. This is unpersuasive because the limitation "assaying the biological activity" is considered to be very broad, and to read on a variety of assays including monitoring the progress of the disease, or toxic effects of the drug, over the course of a series of administrations. For example, Graham monitored the effects of up to 12 sequential doses of modified drug over the course of treatment. Thus Graham measured biological activities of the drug after as many as 11 "booster" doses. Thus the prior art taught the measurement of biological activity, i.e. effectiveness of the drug

and/or toxicity of the drug, after multiple administrations. For these reasons the rejections are maintained.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, John Leguyader, be reached at 571-272-0760. The official central fax

number is 703-872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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DAVE T. NGUYEN
PRIMARY EXAMINER

Richard Schnizer, Ph.D.